REMARKS

Information Disclosure Statement

37 CFR 1.98 (a)(3)

The Office Action states that the information disclosure statement filed May 21, 2002 fails to comply with 37 CFR 1.98 (a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information of each patent listed that is not in the English language.

Presently, the Applicants are obtaining English translations of each patent listed that is not in the English language. These translations will be submitted under separate cover.

37 CFR 1.98 (a)(2)

The Office Action states that the information disclosure statement filed May 21, 2002 fails to comply with 37 CFR 1.98 (a)(2) which requires a legible copy of each U.S. and foreign patent, each publication or that portion which caused it to be listed, and all other information or that portion which caused it to be listed.

Presently, the Applicants are obtaining English translations and legible copies of each patent listed that is not in the English language. These translations will be submitted under separate cover.

Rejection of Claims 1-39 Under 35 U.S.C. § 103(a)

Claims 1-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Masferrer et al. (Survey of Ophthal, 41, 1997, p.S35-S40). The Office Action states that Masferrer et al. disclose that the inhibition of the COX-2 enzyme will lead to the therapeutically desired inhibition of the generation of proinflammtory prostaglandins. Further, the Office Action states that Masferrer et al. also provide motivation to develop and or use selective nonsteroidal COX-2 inhibitors for the treatment of inflammatory diseases, including ocular inflammatory conditions. In addition, the Office Action volunteers that the prior art reference of Masferrer et al. does not recite specific COX-2 inhibitors, but that the skilled artisan is provided with the motivation to develop and or use selective nonsteroidal COX-2 inhibitors to treat ocular inflammatory conditions. In

making these statements, the Office Action is essentially making a *prima facie* argument of obviousness.

The Applicants contend that a case of prima facie obviousness has not been established. "To establish a *prima facie* case of obviousness...the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." (MPEP § 2142). The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte* Clapp, 227 USPQ 972, 973 (Bd. Pat. App & Inter. 1985). The mere assertion in an Office Action of obviousness is not sufficient.

The Applicants point out that not all COX-2 inhibitors are interchangeable. For example, some COX-2 inhibitors show differing activity with respect to other enzyme targets relevant to ophthalmology such as carbonic anhydrase (Zhu, et al. J. Natl. Ca. Inst. 94; 23 Dec 4, 2002). Similarly, all NSAIDs are not effective in the treatment of cystoid macular edema (CME). In fact, a recent publication states that only ketorolac 0.5% has been shown to be effective in the treatment of chronic CME (Clinical Ocular Pharmacology, Blaho, 2001, p 281). The Applicants do not believe that the usefulness of any particular COX-2 inhibitor for any specific ophthalmic condition would be obvious to a person of ordinary skill in the art.

Masferrer et al. address the use of COX-2 inhibitors for therapeutic use for ocular inflammation. However, as pointed out in the Office Action, Masferrer et al do not recite the use of specific COX-2 inhibitors for ophthalmic disorders. The Applicants point out that Masferrer et al give no indication or direction to those skilled in the art as to which of the many possible choices of COX-2 inhibitors are likely to be successful.

Thus, reconsideration and withdrawal of the obviousness type rejection is respectfully submitted.

Rejection of Claims 1-39 Under 35 U.S.C. § 103(a)

Claims 1-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Miyake et al. (PCT Patent Application No. WO 9959634). The Office Action states that Miyake et al. teach the use of selective COX-2 inhibitors to treat ocular inflammation. Moreover, the Office Action states that although Miyake et al. do not recite specific causes of the inflammation, Miyake et al. do in fact teach the skilled artisan of a method of treating inflammation in the eye regardless of its causes. Further, the Office Action states that the skilled artisan would have been motivated to utilize the selective COX-2 inhibitors of Miyake et al. to treat ocular inflammation without regard to its cause. The Office Action states that the generation of prostaglandins is prevented with the administration of COX-2 inhibitors and that for that reason, a variety of diseases and or conditions related to ocular inflammation could be treated with the compounds, which inhibit the generation of proinflammatory prostaglandins, such as with the administration of COX-2 inhibitors.

Miyake et al. claim the use of anti-inflammatory eye drops which contain chemicals selectively inhibiting COX-2 selected from among etodolac, N-(2-(cyclohexyloxy)-4-nitrophenyl)-methanesulfonamide and meloxicam.

The Applicants point out that different ocular inflammatory disorders have different treatments and therefore, it cannot be assumed that COX-2 inhibitors can be used interchangeably to "treat ocular inflammation without regard to its cause" as stated in the Office Action. Because the therapeutic treatment differs for many ocular COX-2 mediated disorders, depending on the ocular disease, the Applicants contend that it would not be obvious to a person of ordinary skill in the art to use any COX-2 inhibitor to treat any ocular COX-2-mediated disorder.

The route of administration of the COX-2 inhibitor also varies depending on the COX-2 inhibitor being used. For example:

> Absorption and distribution to ocular tissues depends on the penetration through the cornea. Drugs that exhibit biphasic solubility penetrate the cornea well. Penetration through the cornea varies with the different species and different ophthalmic NSAIDs (Clinical Ocular Pharmacology; Blaho, 2001, p. 278-279).

> Topical ophthalmic flurbiprofen penetrates the cornea well. In patients having cataract surgery, a preoperative regimen of four drops achieved aqueous humor levels of 120 ng/ml, and a preoperative regimen of 150 mg oral fluribiprofen resulted in levels of 30 ng/ml...Gimbel et al. demonstrated that flurbiprofen penetrates the cornea 20 times more readily than does indomethacin (Id. at 279).

In contrast,

> Indomethacin is a highly insoluble compound. Eyedrops are formulated in an oil-based vehicle or as a 2% suspension or in an aqueous vehicle with a 0.1% concentration. Multiple-drop administration (one drop every 12 hours for 3 days) does not result in accumulation; it is suggested that one drop every 2 to 3 hours might be satisfactory to maintain adequate anterior segment concentration (Id. at 279).

Thus, the use of a specific COX-2 inhibitor for the treatment of ocular disorders as described in the present invention, would not be obvious to one of ordinary skill in the art. One must consider the specific COX-2 inhibitor to be used for treatment, the dosage of that inhibitor, and the route of administration of that inhibitor.

Conclusion

In light of the above, it is respectfully requested that the rejection of Claims 1 through 39, under 35 U.S.C. 103(a) over the teachings of Masferrer et al., and Miyake et al. be withdrawn.

If the Examiner believes a telephonic interview with Applicant's representative would aid in the prosecution of this application, she is cordially invited to contact Applicant's representative at the below listed number.

Respectfully submitted,

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